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(54) Title: TRIAZINES AS APPETITE SUPPRESSOR

(57) Abstract: The invention is directed to using triazine structure containing compounds as an appetite suppressor to induce weight loss.

TRIAZINES AS APPETITE SUPPRESSOR

BACKGROUND OF THE INVENTION

Based on an integration of several very different scientific literatures, including those related to toxicity of herbicides/pesticides, to mechanisms of food intake regulation and anorexia, and to mechanisms of reduced aging and tumorigenesis with diet restriction, a novel use has emerged for chemical compounds that contain the triazine ring structure. Several of these are registered for use in the U.S. as herbicides and pesticides. At certain doses, these compounds have previously been shown to reduce food intake and cause body weight loss. These weight loss effects have invariably been viewed as an indication of toxic side effects.

However, based on the integration of several disparate scientific fields, as noted above, a new possible interpretation has emerged: That triazines may have many of their so-called toxic actions, by a benign process of appetite suppression. This has not been suggested previously in any of the dozens of scientific articles on effects of triazines and metabolites in animals and humans.

A novel use for triazines is suggested by this new integration and interpretation, which is that compounds containing triazine structures may be valuable and useful as appetite suppressants in humans and other mammals.

Atrazine (ATZ) and other chloro-triazines used as herbicides or pesticides are being evaluated for carcinogenic potential, based primarily on a few long-term ATZ-feeding toxicity studies that showed increased incidence of mammary tumors (MTs) in one rat strain and gender: female Sprague-Dawley (SD) rats. Male rats and females of other rat strains or mice of either gender are not susceptible to ATZ induction of MTs, even at very high doses. A series of epidemiological, genotoxocity and endocrine studies have been performed to determine why ATZ induces MTs so selectively in females of the SD rat strain and whether this effect could be relevant to humans.

The most likely explanation that has emerged from these studies is that ATZ acts directly on the hypothalamus-pituitary axis to reduce the release of luteinizing hormone (LH), which results in reduced ovulation and elevated estrogen (E2). The elevated E2 then induces MTs in SD rats. This indicates that the effect is not relevant to humans, since reduced LH in humans and most other species does not result in elevated E2, but rather decreases E2.

The present patent application reviews the literature and concludes that the LH-E2 explanation is probably correct for the Sprague-Dawley rat tumor effect and that ATZ is not a likely carcinogen in humans, a conclusion also reached by an EPA expert panel. In addition, it is claimed herein that ATZ acts primarily as an appetite suppressant.

A number of studies have reported that high dose ATZ causes body weight loss. However, all studies have viewed this as a toxic side effect. The present patent application, for the first time, ties together several other scientific literatures (e.g., on leptin and appetite control, on diet restriction and longevity and on human anorexia) and juxtaposes them with the literature on ATZ, to draw the novel conclusion that ATZ has its effects by benign appetite suppression. Thus, in some circumstances, ATZ could have beneficial or therapeutic actions. these points are summarized below.

Studies of General Carcinogenicity: The epidemiologic studies actually appear to argue very consistently against a role for Atrazine (ATZ) in human carcinogenicity. Two large studies of those apparently most exposed, agricultural chemical production workers, showed decreased mortality from cancers. There have been essentially no statistically significant findings of increased cancers from exposure to ATZ on farms, after exposure for other herbicides/pesticides was controlled for. Thus, the weight of evidence argues strongly against ATZ-induced tumorigenicity and, in fact, raises the possibility that under some conditions ATZ is protective.

The lack of evidence of direct mutagenicity or estrogenicity by ATZ has been shown in a number of studies, and the lack of ATZ-induced tumors in F344 rats or mice of either sex, in male SD rats, or in ovariectomized female SD rats, even at massive ATZ doses far above any seen in humans, further supports the epidemiologic evidence of an absence of ATZ effects on human carcinogenicity.

Mode of Action: There is substantial evidence supporting the conclusion that Atrazine (ATZ) results in elevated estrogen only in female Sprage-Dawley (SD) rats and that this is the mode of action of Atrazine in inducing mammary tumors. There is also substantial evidence for the conclusion that a reduced LH surge is responsible for delayed ovulation and a resulting prolonged estrogen exposure in SD rats. There is also some evidence that ATZ reduces hypothalamic norepinephrine (NE) which could, in turn, reduce release of gonadotrophins (GnRH) and, consequently, luteinizing hormone (LH).

The main evidence supporting this mode of carcinogenicity in SD females arises from long-term toxicology studies showing that male SD rats, and F344 rats or CD-1 mice of either

gender, are insensitive to Atrazine-induced tumors at the Maximum Tolerated Dose (MTD). The MTD is one that induces significant weight loss and is used in most federal toxicity studies (most drugs/substances have a MTD at some level). Further, female SD rats that are normally sensitive to ATZ-induced tumors, are completely insensitive to ATZ if ovariectomized. Thus, there is a requirement for estrogen (E2) in female SD rats for the ATZ effect on mammary tumors (MT). However, although estrogen is necessary, normal levels alone are not sufficient, since the ATZ effect on mammary tumors does not occur in intact female F344 rats or female CD-1 mice.

It has been proposed that the SD vs F344 difference is based on the different patterns of reproductive aging in the two strains, namely that SD rats exhibit reduced LH surges and constant estrous (CE) with elevated E2 production (based on insufficient LH to induce ovulation) whereas F344 rats maintain LH surges in senescence and their ovaries consequently exhibit a diestrous pattern with reduced rather than elevated circulating E2.

The basic mode of action of lower LH and elevated E2 in SD rats suggested above seems highly reasonable, although the evidence of a direct ATZ effect on hypothalamic GnRH release is questionable. The evidence of ATZ actions on NE is based on very high concentrations of ATZ; therefore, this third link of the proposed mode is clearly not as well documented as the LH and E2 link.

Alternative Mechanism of ATZ Effects on the LH Surge. However, one major likely alternative mechanism of reduced LH that could account for most of the ATZ effects, but which has as yet apparently not received consideration, are the dramatic effects of ATZ in reducing food intake and body weight even at much lower doses than are usually studied for potential carcinogenicity. Essentially every study to date has shown that at the moderate or high doses of ATZ that induce MTs in SD rats, or induce any toxicity for that matter, there is substantial weight loss associated with reduced food intake.

However, it is also well known that reduced food intake and weight loss is a potent stimulus for reduced LH secretion in humans or rats. Even mild nutritional restriction results in reduced LH and functional hypothalamic amenorrhea (Cousinet et al, Clin. Endocrinol. 50:229-235, 1999). For example, leptin, which is produced by adipose cells, normally stimulates FSH and LH in females (Walczewska et al, Proc. Soc. Exp. Biol. Med. 222:170-177, 1999). Anorexia or other low body fat conditions (e.g., from exercise) directly reduce leptin and are strongly associated with human amenorrhea (Kopp et al, 1997, Mol. Psychiatry, 2:335-340). Leptin appears to coordinate nutritional requirements for fetal growth and nutritional restriction

inhibits reproduction in part by lowering leptin (Holness et al, Mol. Cell Endocrinol. 157:11-20, 1999). These references are incorporated by reference in their entirety.

Thus, there is no evidence of carcinogenicity in humans. However, there remains a long felt but unresolved need for an effective composition and method for suppressing appetite for those who need to lose weight for health reasons or for aesthetic reasons. ATZ may be useful as an appetite suppressant at low doses.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a composition and method for suppressing appetite in an individual in need thereof.

Another object of the present invention is to make available a composition and method for suppressing appetite in healthy individuals.

The invention is also directed to a pharmaceutical composition comprising an appetite suppressing amount of a triazine compound optionally in combination with a pharmaceutically acceptable excipient.

The invention is directed to an appetite suppressant composition that is administered to an individual for the intended effect as an appetite suppressant in a pharmaceutical format, and not as a test compound.

The invention is directed to a method for inducing weight loss in mammals comprising administering a composition comprising a triazine ring structure containing compound, including triazine metabolites. The mammal may be a human being, and the inducing of weight loss may be caused by appetite suppressive effect of said composition.

In the inventive method there is a minimal or no serious toxic side effect seen in the mammal.

Additional aspects, features, embodiments and advantages of the present invention will be set forth, in part, in the description that follows, or may be learned from practicing or using the present invention. The objects and advantages may be realized and attained by means of the features and combinations particularly pointed out throughout this description, the referenced drawings attached hereto and the appended claims. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not to be viewed as being restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given hereinbelow, and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, and wherein;

Figure 1 shows structures of atrazine and major metabolites;

Figure 2 shows structure of the amino-s-triazine ring;

Figure 3 shows structure of chlorsulfuron; and

Figure 4 shows structures of simazine and propazine.

DETAILED DESCRIPTION OF THE INVENTION

It is suggested here that reduced food intake is a primary mechanism of the effect of ATZ in all rats. This apparently leads to mammary tumors only in those rat strains that are excessively obese from continued growth and/or that respond to reduced nutrition with a rapid fall off of LH and elevated E2. That is, it appears that elevated E2 may be required for the MT effect. It might also be that only obese strains of rat exhibit a reduced LH surge with aging.

This view does not preclude a role for an ATZ action in the hypothalamus since the mechanism through which ATZ reduces appetite and food intake may still be somehow mediated by eating control systems in the hypothalamus. However, if this body weight interpretation is correct, it argues for a novel mode of action in the brain, as follows:

1. ATZ → 2. Brain (Hypothal? Midbrain? Limbic system?) → 3. Appetite Suppression → 4. Weight Loss → 5. Reduced Adiposity → 6. Reduced Leptin (or other signal) → 7. Reduced LH and an Elevated Estrogens (in some rodents only)

In this view, the originally proposed reduced LH-elevated estrogen mode of ATZ-induced MTs in SD rats is still valid. The major difference here is in the sequence of events that trigger the initial LH reduction. Instead of a toxic hypothalamic-pituitary action of ATZ, it is suggested here that ATZ acts to reduce food intake and body weight by benign appetite suppression. In this novel view, therefore, loss of body weight is not necessarily a sign of toxicity, but rather, a potentially harmless, or even useful, effect in most animals and in humans.

Other Toxicity Effects. If body weight is a key factor in ATZ effects on MTs, this could account for many of the other reported miscellaneous toxic effects of high dose ATZ on endocrine and physiological variables. That is, dramatically reduced food intake induced by

high dose gavage studies (for 3-12 days in rats which, in proportion of lifespan, might be equivalent to 3 to 12 months of human life) could result in anorexia and rapid weight loss in the rats and, consequently, altered androgen synthesis, reduced testes or liver weight, low weight fetuses, liver function changes, etc.

Relevance of Neuroendocrine Mode to Humans. Reduced LH does not result in elevated estrogens in humans. Unlike the rat, which has many developing follicles in each estrous cycle, humans typically have one developing follicle per ovulation cycle. Moreover, humans lose ova with age, and human female reproductive senescence, like that of the F344, is well established to be associated with reduced circulating estrogens.

As noted above, there does not seem to be a clear rationale for the proposal that if effects of ATZ on pituitary LH occur in humans as in SD rats, then amenorrhea and non-ovulating follicles might occur. Two acyclic human syndromes with some aspects of impaired pituitary regulation have been compared to ATZ effects: human hypothalamic amenorrhea (HA), which can result from exercise, stress or weight loss, among other factors, and polyastic ovarian syndrome (PCOS), which is characterized by elevated LH and E2 output (Sir-Petermann et al, Hum. Reprod. 14:1435-1439, 1999), which is incorporated by reference herein in its entirety.

However, PCOS is clearly not a good model of the ATZ MT effect in SD rats, because it is produced by elevated, not reduced, LH. Obviously, none of the ATZ effects reported to date would induce an elevated LH mode of action similar to that seen in PCOS.

Similarly, HA is associated with normal to decreased E2 (most studies find it decreased, e.g., Cousinet et al, 1999, see above), so the elevated E2-mediating mechanism of MT induction in SDs would be absent even if ATZ induced lower LH resulting in HA.

Moreover, the data showing a direct effect on NE are not robust because of the high doses required and because of ATZ induction of higher dopamine and reduced prolactin, which should protect against MTs and is inconsistent with the proposed mode of action.

As noted, a more likely explanation than a direct action on hypothalamic GnRH regulation is an effect on appetite. At the extreme, this can also trigger a similar cascade of reduced GnRH and LH.

There is apparently no clear, established or even likely neuroendocrine path through which ATZ could induce cancer in humans, whether by a mode similar to that in SD rats or direct estrogenic actions. Rather, reduced food intake is likely a primary mechanism of the effect of ATZ in humans.

It is also contemplated that the mode of weight loss that occurs as a consequence of administering the triazine compounds to mammals, including humans, is by a pathway different from appetite suppression. Metabolic or any other biochemical effects of the triazine compounds are contemplated that cause weight reduction while causing little negative side-effects.

Atrazine belongs to a class of compounds known as triazine in reference to the triazine ring structure that they contain. Several compounds containing triazine rings are presently registered for use in the U.S. as pesticides. Many of these pesticides (but not all) will have nitrogen atoms attached to carbon two and four. Compounds with this moiety are more appropriately referred to as "amino-s-triazines." These triazine-containing chemicals can be divided into several classes of compounds: sulfonylurea-triazine compounds (that do not have the nitrogen at C2 and 4; alkyamino, alkythio-triazines and chloro-triazines. Atrazine is a chlorotriazine. The distinction between the chemical classes lies in the groups attached to the R1 position of the triazine ring (C6). Chloro-triazines will have chlorine atom at the R1 position. The alkyamino-triazines will have an alkyamino moiety at R1 and the alkoxy will have a hydroxyl moiety at R1. Sulfonylurea compounds will have at R2, a sulfonated urea moiety to which another structure, frequently a benzene ring, is attached. The structures of atrazine and several atrazine metabolites are shown in Fig. 1. The structures of the amino-s-triazine ring itself and of chlosulfuron, a representative example of a sulfonylurea compound, are shown in Fig. 2 and Fig. 3. The structures of the chloro-triazine pesticides simazine and propazine are shown in Fig. 4.

For purposes of the present invention, it is understood that the various R groups, such as R1, R2, and R3 moieties, may be any chemical substituent at all, so long as the triazine ring containing compound retains benign appetite suppressing activity.

Two-year bioassay studies using female Sprague-Dawley rats have been performed on several of the triazine compounds. As shown in Tables 1 and 2, bioassay results demonstrate that the triazine ring structure, in and of itself, is not carcinogenic for mammary tumors in the female Sprague-Dawley rat (Spencer, 1991). Not shown in Tables 1 and 2 are the results from five two-year bioassays using sulfonyurea compounds. Four out of the five studies with sulfonyurea compounds were negative for carcinogenicity. The fact that four out of five sulfonyurea and three out of for alkyl amino, alkoxy, or alkythio-triazine compounds failed to induce tumors, including mammary tumors, in SD rats indicates that simply containing a triazine ring is not sufficient to render a compound carcinogenic. Chlorine at the R1 position seems to promote an

increased carcinogenic potential. For example, all four of the chlorotriazine compounds are able to induce mammary tumors but only in female Sprague-Dawley rats.

Table 1. Results of Two-Year Bioassays with Alkylamino, alkoxy, and alkythio-triazine Compounds

Chemical	Species/Strain	Results	Reference
Cyromazine R1-NH_2	Rat-Sprague-Dawley	Negative for oncogenicity in doses up to 3000 ppm	Blair et al., 1981
Prometryn R1-SCH_3	Rat-Sprague-Dawley	Negative for oncogenicity in doses up to 1500 ppm	Chau et al., 1991
Terbutryn R1-SCH_3	Rat-CD®BR (SD rats)	Positive for female mammary tumors at 3000 ppm	Wood, 1979
Prometon R1-OCH_3	Rat-Sprague-Dawley	Negative for oncogenicity in doses up to 1000 ppm	O'Connor et al., 1988

Table 2. Results of Two-Year Bioassays with Chloro-triazine Compounds

Chemical	Species/Strain	Results	Reference
Atrazine R1-Cl	Rat-Sprague-Dawley	Positive for female mammary tumors at 70 ppm	Mayhew et al., 1986
Simazine R1-Cl	Rat-Sprague-Dawley	Positive for female mammary tumors at 100 ppm	McCormick et al., 1988
Propazine R1-Cl	Rat-Sprague-Dawley	Positive for female mammary tumors at 3 ppm	Jessup, 1980a
Cyanazine R1-Cl	Rat-Sprague-Dawley	Positive for female mammary tumors at 5 ppm	Bogdanffy, 1990

Of special interest when looking at structural analogues of atrazine is the functional similarity between those compounds most similar to atrazine (simazine, propazine and cyanazine) in regards to carcinogenicity. Like atrazine, all three of these compounds are positive for mammary tumors in the female Sprague-Dawley rat (see Table 2) and all three have been tested in two-year mouse bioassays and have been found to be negative for carcinogenicity (Hazelette and Green, 1988; Jessup, 1980b; Gellatly, 1981). Like atrazine, genotoxicity studies with simazine and propazine do not support a mutagenic potential for these compounds. Mutagenicity studies with cyanazine have yielded mixed results, although the presence of the cyano group in cyanazine confounds comparison of this compound with the three other chloro-s-triazines relative to mutagenicity.

Thus according to another aspect, the invention relates to pharmaceutical compositions containing an effective amount of a compound of triazine, mixed with suitable pharmaceutically acceptable excipients.

The usual, necessary daily dose of the compound according to the invention will be in the range of 0.001 to 1 mg/kg of body weight per day of the active compound of a triazine. Most conditions respond to a treatment comprising a dosage level in the order of 0.002 to 0.2 mg/kg of body weight per day. Thus, for administration to a 50 kg person, the dosage range would be about 1 mg per day, preferably between about 0.1 to 10 mg per day.

Depending on the specific clinical status of the disease, administration can be made via any accepted systemic delivery system, for example, via oral route or parenteral route such as intravenous, intramuscular, subcutaneous or percutaneous route, or vaginal, ocular or nasal route, in solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, cream, gel, implant, patch, pessary, aerosols, collyrium, emulsions or the like, preferably in unit dosage forms suitable for easy administration of fixed dosages. The pharmaceutical compositions will include a conventional carrier or vehicle and a triazine compound and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, and so on.

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, and so on.

The compounds of this invention are generally administered as a pharmaceutical

composition which comprises a pharmaceutical vehicle in combination with a triazine compound. The amount of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about 0.01 weight percent (wt %) to about 99.99 wt % of the drug based on the total formulation and about 0.01 wt % to 99.99 wt % excipient.

The preferred mode of administration, for the conditions mentioned above, is oral administration using a convenient daily dosage regimen which can be adjusted according to the degree of the complaint. For said oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of the selected triazine compound in any of the currently used excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talc, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between 0.01 wt % and 99.99 wt % of the active compound according to this invention.

Preferably the compositions will have the form of a sugar coated pill or tablet and thus they will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as starch, polyvinylpyriolidone, acacia gum, gelatin, cellulose and derivatives thereof, and the like.

It is understood that by "pharmaceutical composition", it is meant that the triazine compound is formulated into a substance that is to be administered purposefully for reducing weight of the individual. The mode of action is believed to be by appetite suppression. However, it is understood that the triazine compound per se will not have a toxic effect, and by "pharmaceutical composition", it excludes those compositions that are used to administer to individuals as test compounds for a purpose other than as an inducer of weight loss.

All of the cited references are incorporated herein by reference in their entirety.

* * * * *

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention specifically described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A pharmaceutical composition comprising a triazine ring structure containing compound and a pharmaceutically acceptable excipient thereof.

2. The pharmaceutical composition according to claim 1, wherein said triazine ring structure containing compound is atrazine, its major metabolites, amino-s-triazine containing compound, chlorsulfuron, simazine, propazine, or cyanazine.

3. An appetite suppressant pharmaceutical composition comprising a triazine ring structure containing compound and a pharmaceutically acceptable excipient thereof.

4. A method for inducing weight loss in mammals comprising administering the composition according to claim 1 to a mammal in need thereof.

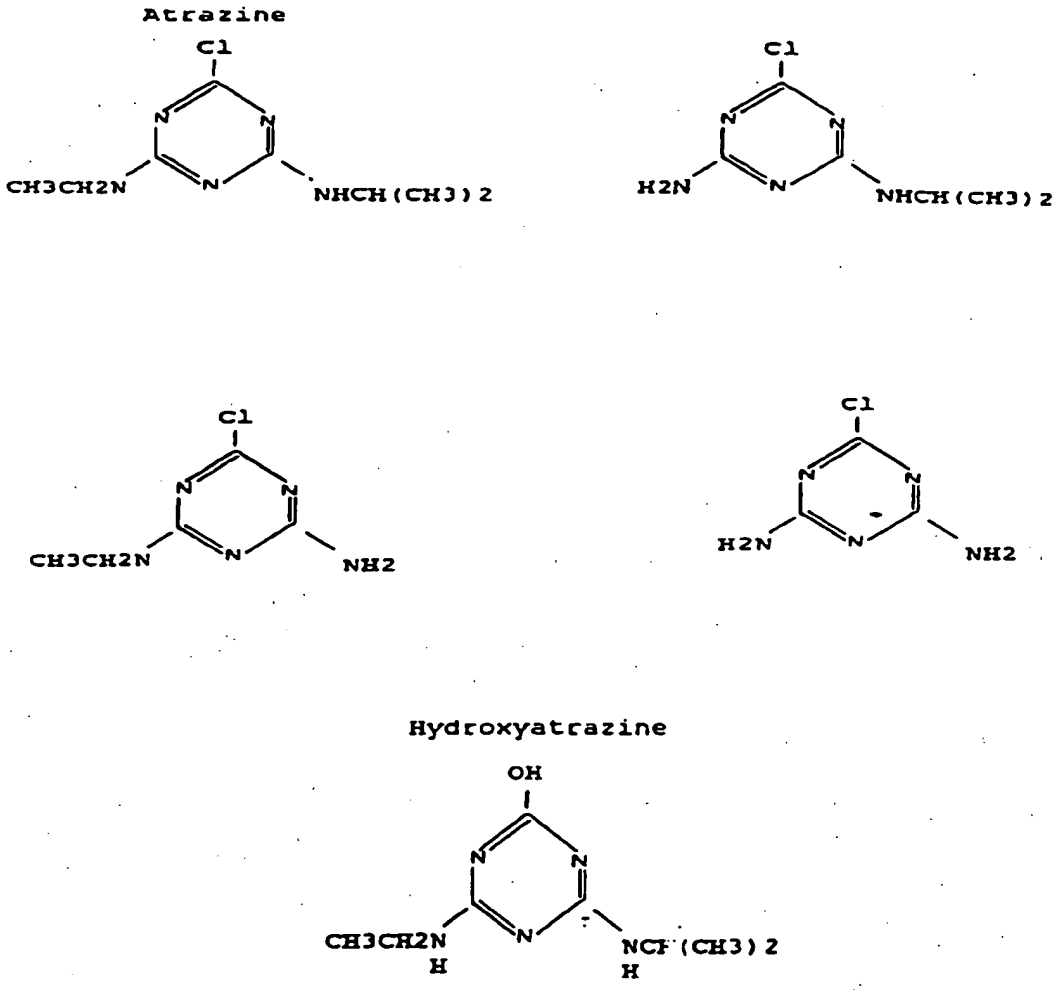
5. The method according to claim 4, wherein said triazine ring structure containing compound is atrazine, its major metabolites, amino-s-triazine containing compound, chlorsulfuron, simazine, propazine, or cyanazine or other triazine analogues.

6. The method according to claim 4, wherein said mammal is a human being.

7. The method according to claim 4, wherein a minimal or no serious toxic side effect is seen in said mammal.

8. The method according to claim 4, wherein said inducing of weight loss is caused by appetite suppressive effect of said composition comprising a triazine ring structure containing compound.

FIG. 1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NH2
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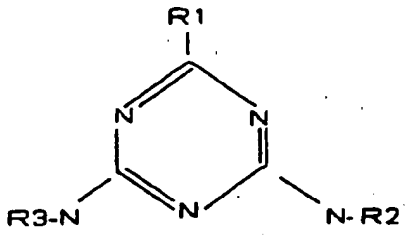
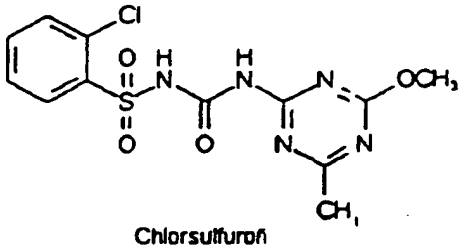
H

FIG. 2



Amino-s-Triazine Ring

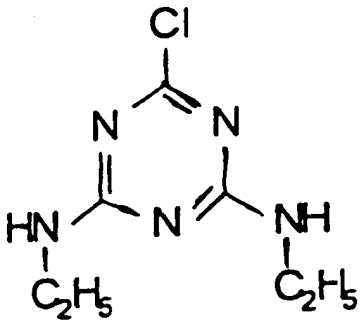
FIG. 3



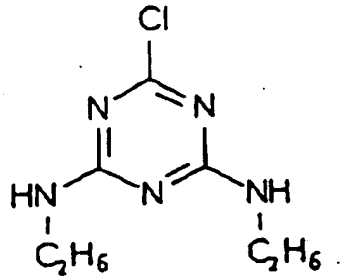
Chlorsulfuron

FIG. 4

Simazine



Propazine



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/03057

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/53
US CL :514/241, 245
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/241, 245

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST
simazine, triazine, propazine, atrazine, chlorsulfuron, weight loss, appetite suppression

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,965,281 A (CUOMO et al.) 23 October 1990, see abstract, col. 2, lines 15-38, col. 3, line 40 to col. 5, line 49.	1-3
A	US 5,597,797 A (CLARK) 28 January 1997, see entire document.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search
12 MARCH 2001

Date of mailing of the international search report
12 APR 2001

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Form PCT/ISA/210 (second sheet) (July 1998)*